**SUMMARY MINUTES**

# MEETING OF THE ORTHOPAEDICS AND REHABILITATION DEVICES ADVISORY PANEL

**OPEN SESSION**

**JANUARY 10, 2002**

**Meeting of the Orthopaedics and Rehabilitation Devices Advisory Panel**

**Attendees**

January 10, 2002

*Acting Chairperson*
Maureen Finnegan, M.D.

*Executive Secretary*
Hany Demian, M.S.

*Members*
Barbara D. Boyan, Ph.D.
Betty Diamond, M.D.
John Doull, Ph.D., M.D.
Edward N. Hanley, M.D.
John Kirkpatrick, M.D.
Leon Lenchik, M.D.
Stephen Li, Ph.D.
Sanjiv Naidu, M.D., Ph.D.
A. Hari Reddi, Ph.D.
Gene P. Siegal, M.D., Ph.D.

*Guests*
John Kostuik, M.D.
Richard K. Miller, Ph.D.
Rocky Tuan, Ph.D.

*Consultants*
Kinley Larntz, Ph.D.

*Consumer Representative*
Karen Rue

*Industry Representative*
Sally Maher, Esq.

*FDA Representative*
Celia Witten, M.D., Ph.D.

**CALL TO ORDER**

Executive Secretary Hany Demian called the meeting to order at 9:40 a.m. He stated that panel consultants Kinley Larntz, Sanjiv Naidu, Leon Linchik, Gene Siegal, John Kirkpatrick, Barbara Boyan, John Doull, Betty Diamond, and Hari Reddi had been granted temporary voting status and that Maureen Finnegan had been appointed acting chairperson for the duration of the meeting. In addition, Drs. Li, Larntz, Hanley, and Kirkpatrick had been granted conflict-of-interest waivers for their interests in firms that could potentially be affected by the outcome of the panel's deliberations; they therefore could participate fully in the meeting. Matters involving Drs. Li, Larntz, Finnegan, Boyan, and Siegal had been considered and were deemed unrelated to the topic at hand; those members' full participation was therefore permitted. Dr. Hanley had past involvement in matters related to the day's agenda and could therefore participate in panel discussions but not vote. Panel guests Tuan and Kostuik had interests in the firm at issue. Mr. Demian asked the panelists to introduce themselves and then turned the meeting over to Acting Chair Finnegan.

Dr. Finnegan stated that that the purpose of the meeting was for the panel to make recommendations on a premarket approval application (PMA) for a spinal fusion cage with a growth factor soaked in a collagen sponge used to treat lumbar degenerative disk disease (DDD). She noted that the panel members constituted a quorum.

**OPEN PUBLIC HEARING**

Patsy Trisler, senior director, PharmaNet Consulting, stated that although bone morphogenetic proteins (BMPs) are an important advance, it is important to be certain that all questions have been addressed in the approval process. She expressed surprise that the FDA had agreed that certain nonclinical safety studies could be conducted postapproval. If transformed cells or other adverse events are seen after the implant has been released to the market, what is the surgeon to

tell the patient? The panel should give special attention to the potential for off-label use for the device at issue.

John McCullough, M.D., an orthopedic surgeon from Denver, CO, stated that he had been a participant in the pilot study of the device. The success of the device is well established by research. The FDA should require the device components to be packaged together to help minimize the potential for off-label use.

Executive Secretary Hany Demian then read eight letters into the record:

?? Regis W. Haid, M.D., The Emory Clinic, Atlanta, GA, asked the panel to expedite the approval of the device. He stated that BMP offers a significant advantage for physicians and would eliminate the pain, complications, and additional expense associated with the harvest of autograft iliac crest.

?? David G. Malone, M.D., F.A.C.S., Oklahoma Spine & Brain Institute, stated that BMP may lead to excessive bone growth and may cause significant neural impingement if placed in a posterior lumbar interbody type of device. He stated that if BMP is approved for spinal fusion, it would be useful to require that the device be placed in such a manner that bone overgrowth cannot protrude into the spinal canal.

?? Robert J. Banco, M.D., chief, Spine Section, New England Baptist Hospital, wrote that BMP supplants the need for harvesting the iliac crest and reduces the risk of associated complications, including pain, infection, nerve damage, and possible damage to the muscle and vessels.

?? Paul C. McCormick, M.D., professor of clinical neurological surgery, Columbia Presbyterian Medical Center, New York, also noted the complications associated with the harvesting of

autograft. Any useful adjunct that can facilitate and enhance spinal fusion would be of tremendous benefit to patients.

?? J.J. Abitbol, M.D., California Spine Group, San Diego, CA, said that BMPs are a safe new alternative to taking autograft and urged the panel to approve their use.

?? John H. Peloza, M.D., Center for Spine Care, Dallas, TX, described the different types of bone graft material and their limitations. He outlined the advantages of rhBMP-2 and urged the FDA to move it into clinical use.

?? Stephen M. Papadopoulous, M.D., Curtis A. Dickman, M.D., and Volker Sonntag, M.D., Barrow Neurological Associates, Phoenix, AZ, stated that approval of BMP would provide a significant advance for patient outcome and satisfaction following spinal fusion.

?? Dr. Douglas Moreau **[sp?]** wrote that he is both a physician and patient and has been delaying his own spine surgery pending approval of the device. He urged approval of the device.

**SPONSOR PRESENTATION**

Bailey Lipscomb, Ph.D., vice president, clinical affairs, Medtronic Sofamor Danek, outlined the main characteristics of the InFUSE Bone Graft/LT-CAGE Lumbar Tapered Fusion Device (hereafter, the InFUSE device). The InFUSE device has three components: a metal spinal fusion device (i.e., cage), an absorbable collagen sponge (ACS), and recombinant human BMP-2 (rhBMP-2) solution. The cage and the ACS already have been approved by the FDA. Dr. Lipscomb described how the device is used and emphasized that the issue before the panel was not the metal cage or ACS but the safety and efficacy of rhBMP-2 as a replacement for current bone graft sources.

Gerard Riedel, Ph.D., Wyeth-Genetics Institute, Cambridge, MA, summarized the

sponsor's biological and preclinical safety data. After describing the manufacturing process of rhBMP-2, he outlined some of its properties. Endogenous BMP-2 is active in bone repair and embryonic development and induces bone growth both in humans and in animals. Dr. Riedel described the cell biology underlying the mechanisms of BMP-2 and noted that implantation of rhBMP-2 requires a matrix (in this case, ACS) to deliver the protein to the site and retain it there long enough to allow bone formation. Dr. Riedel provided data describing the extent to which ACS augments rhBMP-2 retention at the implantation site.

Dr. Riedel then presented data from implant safety studies; absorption, distribution, metabolism, and excretion (ADME) studies; and tumor biology, systemic toxicity, and reproductive toxicity studies. He stated that the data demonstrate that the device is safe. Results of implant studies results found no systemic effects. Biodistribution studies in rats and rabbits found that rhBMP-2 is released slowly from the implant site and has low systemic availability. ADME studies found that the protein is cleared rapidly from the circulation—primarily through the liver—and is rapidly degraded and excreted into urine.

Although some tumors express BMP-2 and have BMP-2 receptors, tumor biology studies found no evidence that rhBMP-2 initiates tumors. No cytotoxic or mutagenic activity was found in vitro, and no evidence of abnormal cell biology was found in implant toxicity studies. In vitro testing of 51 tumor cell lines resulted in growth promotion in 3 lines (2 pancreas, 1 prostate) and no effect on the remaining 48. Of 71 primary tumor isolates tested, either no effect or inhibition occurred, but inhibition was not sufficient for therapeutic use. Following consultation with FDA, the sponsor has agreed to carry out additional tumor studies.

Toxicity studies in rat and rabbit models using 1,000 times the human rhBMP-2 dose found no systemic effect. Reproductive toxicity studies also found no systemic effects. Riedel

summarized additional studies designed to gain a better understanding of the immune response to rhBMP-2 that were planned in consultation with FDA.

Scott Boden, M.D., professor of orthopaedic surgery and director of the Emory Spine Center at the Emory University School of Medicine, summarized the preclinical and pilot clinical studies on the InFUSE device. Animal studies found that the fusion rate at 3 or 6 months followup was considerably greater with cages using the protein than with cages not using the protein. Biomechanical test results found no statistical difference in bone stiffness of autograft and rhBMP-2 fusions. Bone strength relative to adjacent bone also showed no statistical difference for autograft and rhBMP-2 fusions. In primates, devices using the ACS without rhBMP-2 showed no fusion at 6-month followup.

Dr. Boden said that the pilot clinical study results revealed significantly greater rates of fusion as well as lower Oswestry Low Back Pain Disability Questionnaire pain scores with the InFUSE device than with autograft. He presented several slides illustrating the differences in fusion between patients with the InFUSE device and autograft controls.

Dr. Boden summarized the data by saying that the device is safe: No bone formation occurred away from the cages. In addition, the device is effective because it eliminates bone-grafting morbidity and has equal or better healing success. The bone formed is normal and biomechanically equal to autograft. CT scan analysis correlated well with histological analysis of rhBMP-2 bone formation.

Hallet H. Mathews, M.D., an orthopedic surgeon from Richmond, VA, presented the clinical trial results for the InFUSE device. The study had a prospective, randomized controlled design and took place at 16 investigational centers. The patients in the treatment group received the InFUSE device; the control patients (i.e., the *autograft group*) received cage devices filled

with autogenous bone harvested from the iliac crest. Patients in both groups had similar demographic characteristics and preoperative medical conditions. A total of 143 patients received the InFUSE device; 136 patients were treated with autogenous bone graft. Patient follow-up compliance at all postoperative periods exceeded 90%.

Success was measured in terms of *Overall Success*, a derived variable encompassing primary safety and effectiveness considerations; it was the primary endpoint for the entire study for PMA approval purposes. The variable comprised the effectiveness parameters of fusion, Oswestry Questionnaire scores, and neurological success. It also was influenced by two safety considerations: the occurrence of any serious adverse event possibly associated with the device and the occurrence of a second surgical procedure classified as failure. The Overall Success rates for the two treatment groups were statistically equivalent at 24 months. The primary clinical trial objective was met, thus supporting approval of the product.

Safety was assessed as a function of the nature and frequency of adverse events and second surgery procedures and the formation of antibodies to rhBMP-2 and collagen. The InFUSE group was found to be as safe as the autograft group.

No statistical differences were found between the two groups for all categories of adverse events, except for graft-site events and urogenital complications. Nearly 6 percent of the autograft patients had a graft site complication, including bone fractures, nerve injuries, infection, and hematoma. No graft site adverse events occurred for the InFUSE group because the device eliminates the need to harvest bone graft. The differences in the urogenital complication rates were mainly due to urinary retention following surgery; those problems resolved in all patients prior to their discharge from the hospital. The second surgery rates for both groups were comparable; no statistical differences were found for any of the categories of

additional surgery.

Both computed tomography (CT) scans and x-rays were used to assess fusion, and Mathews described the assessment process and criteria. At 24 months following surgery, the InFUSE fusion rate was statistically equivalent to the autograft rate.

The Oswestry Questionnaire was used to measure the effects of back pain on a patient's ability to manage everyday life. The mean Oswestry scores for the two treatment groups were similar at all time periods. In addition, the 24-month neurological success rates for both groups were statistically equivalent. Other outcome measures included back pain, leg pain, disc height maintenance, and general health status as measured by the SF-36 survey. The 24-month results were comparable for the two treatment groups; statistical equivalence between treatments was demonstrated for all but back pain and the mental component summary of the SF-36.

Another arm of the clinical trial examined the laparoscopic implantation of the InFUSE device. Dr. Mathews stated that those data augment the safety profile of the device and support approval of that implantation method. Compared with the patients in the open study, the hospital stay for the 134 laparoscopic patients was approximately 2 days shorter on average, a finding that was statistically significant. Nearly 45 percent of the laparoscopic patients were treated on an outpatient basis, compared with virtually none of the patients in the other two groups; they also returned to work an average of 20 days sooner. The Overall Success rate at 24 months following surgery for the laparoscopic patients was greater than 68 percent—nearly 12 percentage points higher than and statistically superior to that of the autograft rate of approximately 56 percent.

Dr. Mathews finished by showing slides of CT scans from some of the study patients. He stated that CT scans are the best method for detecting new bone formation within cages and

determining fusion status.

Bailey Lipscomb, Ph.D., Medtronic Sofamor Danek, concluded by saying that the sponsor has demonstrated a reasonable assurance of safety and effectiveness. He addressed the FDA's questions to the panel and noted that the evidence indicates that rhBMP-2 has either no effect or an inhibitory effect on tumor cell proliferation. No scientific evidence suggests that rhBMP-2 transforms a normal cell into a tumor cell. Neither preclinical animal studies nor human clinical trials have found problems involving the effects of antibodies to rhBMP-2 on fetal development. The issue can be adequately addressed through labeling statements and instructions to female patients of childbearing age.

**FDA PRESENTATION**

Aric Kaiser, M.S., PMA lead reviewer, described the components of the InFUSE device and summarized the areas of concern to the FDA: reproduction and teratogenicity, tumorigenicity, radiographic effectiveness, instructions for use, and postmarket studies.

Peter L. Hudson, biologist, Division of General, Restorative, and Neurological Devices, Office of Device Evaluation, Center for Devices and Radiological Health, listed some of FDA's concerns with the InFUSE device and said that the sponsor has begun to address those concerns by adding studies to the postmarket review process. The FDA is particularly concerned with rhBMP-2's potential to stimulate transformed cells and the potential for an immune response to rhBMP-2 to cause adverse effects. The systemic availability of rhBMP-2 is low and that minimal exposure to the protein occurs outside the implantation site; rhBMP-2 is rapidly cleared from the body through a renal pathway. The preclinical evaluations on carcinogenicity, however, are not sufficient to reveal the protein's effects on tumorigenesis. In the sponsor's studies, no adverse clinical effects were correlated with positive antibody formation. The FDA is concerned about

the potential for an immune response to cause adverse effects on embryogenesis and maternal immune response. Data from studies of BMP knockout mice indicate that fetal defects are possible. Additional animal studies should be conducted to investigate the potential of rhBMP-2 antibodies to cause teratogenic effects and adverse immunologic effects in women. A registry for women of childbearing age might be useful.

Barbara Buch, M.D., clinical reviewer, highlighted key points from the FDA's clinical review. She reviewed the sponsor's findings from the clinical trial and noted that the study was well conducted. The significance of the antibody findings cannot be determined. Regarding adverse events, incidents of pain, hematoma, and infection at the donor site occurred only in the control group. The rates of urogenital, retrograde ejaculation, and graft site-related adverse events are of concern: The investigational group had a higher rate of migration and malpositioning of devices than the control group; the control group had higher rates of loosening and displacement and subsidence than the investigational group. The two groups were equivalent in cysts found inferior to the implant. On the whole, however, the two groups had equivalent clinical effectiveness and safety; in addition, the InFUSE device avoids donor-site morbidity. Concerning radiographic interpretation of the data, one may not be able to extrapolate animal data to potential human responses.

Telba Irony, Ph.D., mathematical statistician, Division of Biostatistics, summarized the FDA's statistical analysis. The experimental treatments (i.e., laparoscopic and open surgery) were likely to produce results at least equivalent to those of the control group. Dr. Irony presented a statistical comparison of the use of x-rays and CT scans in assessing spinal fusions in the sponsor's study and concluded that sensitivity and specificity were better for CT scans than for x-rays. In no case was the presence of bridging bone detected by x-ray and not by CT scan.

Less disagreement was found at 24 months than at 12 months. The relevant endpoint for this PMA is fusion at 24 months.

Rocky Tuan, chief, Cartilage Biology and Orthopedics Branch, National Institute of Arthritis, Musculoskeletal, and Skin Diseases, described the biology of BMPs, including their molecular structure and mechanism of action, biological activity, and issues related to biological complications. BMP is highly cell specific: The same BMP can do different things to different cells. During development, BMPs are crucial for the fetus; ample evidence indicates that if BMP genes are deleted, it is lethal to the embryo. After birth, BMPs play a role in fracture repair, spine fusion, defect healing, and osteointegration. After implantation in a site, distribution of rhBMP-2 is limited; a low systemic level is found. Much is still not known about tumor induction, hematological perturbations, teratological effects (particularly whether they could be transgenerational), and immunoreaction.

Richard K. Miller, Departments of Obstetrics/Gynecology, Environmental Medicine, and Pathology, University of Rochester Medical Center, Rochester, NY, presented an overview of teratology and developmental toxicology. He outlined the minimum requirements for reproductive toxicity studies and described the process of human risk assessment in reproductive toxicology. Dr. Miller concluded by describing what pregnancy registries can do, when they should be constructed, how they should be designed, and their timing and scope. The window of opportunity for collecting reports is in the first 5 years of marketing. Registries are not likely to be useful for agents on the market for an extended period of time due to the diminution of voluntary reporting.

John Kostuik, M.D., director of spinal surgery, Johns Hopkins University, discussed issues involving assessment of spinal fusion. CT scans could be more useful with the sponsor's

product than with autograft. One of the most telling ways to determine fusion is through the radiolucency around a device—any lucency means nonunion if the patient still has pain. Bone scans have little value—most fusions are warm for 24 months; warmth for longer periods than that indicates pseudarthrosis. The best indication of fusion is the presence of anterior sentinel graft, but it is unclear how thick that should be.

**Panel Preclinical Review—A. Hari Reddi, Ph.D.**
Dr. Reddi noted that BMPs are natural substances that are found in mammals as well as other organisms. BMPs are normal constituents in the body; excessive worries about teratogenicity are unwarranted.

**Panel Clinical Review—John Kirkpatrick, M.D.**
Dr. Kirkpatrick observed that DDD is a fairly controversial subject. Many people have DDD without pain; fusion is for the treatment of back pain, not the disease. The patient populations in the clinical trial were similar. Nothing in the sponsor's data indicates a problem, but it is unclear why bovine antibodies were found in the control group. The InFUSE device is as safe as using autograft.

**Panel Statistical Review—Kinley Larntz, Ph.D.**
Dr. Larntz extended his compliments to the sponsor and FDA for the clear presentation and the quality of the data. The device clearly meets the criteria set forth in the protocol. Some kind of sensitivity analysis is needed: A number of measures are scales, and the analysis summarized outcomes as success or failure. Information is lost when using arbitrary cutpoints. The laparascopic patients differed in several ways from the patients in the other two groups—the results should have been adjusted for the patient populations.

Mr. Kaiser then read the questions before the panel.

**PANEL DISCUSSION**

Panel members summarized their questions and concerns about the InFUSE device. Many members extended compliments to the sponsor on the quality of the research. Company representatives answered each panel member's questions in turn.

Dr. Li asked whether any agents had passed all in vitro testing but were later found to have tumorigenetic effects or to create birth defects. Dr. Riedel said that to the best of his and his colleagues' knowledge, there was not such an agent. Dr. Miller said that certain estrogens, such as diethylstilbestrol, fell into that category. Dr. Li asked for clarification regarding the definition of bridging bone, which the sponsor answered to his satisfaction. He also asked whether radiographic evidence was predictive of clinical success or failure. Harry Genant, M.D., University of California, San Francisco, a paid consultant to the sponsor, said that radiographic evidence was not strongly correlated with clinical success. No determination had been made with regard to the minimum amount or thickness of bridging bone necessary to be considered clinically relevant. Dr. Riedel added that it was not uncommon to have persistent symptoms not in accord with radiographic images. Dr. Li asked whether any animal or other data correlated the amount of bridging bone and biomechanical measurements; Dr. Riedel provided additional information on the biomechanical properties of the bone formation in the animal studies.

Dr. Doull noted that Dr. Hudson had stated that much variability among species existed in the effects of a given dose of rhBMP-2. In such situations, intraspecies variability often exists as well. Dr. Riedel provided additional information, saying that the local concentration correlates with the efficacy within species, a relationship that is consistent across all anatomic sites within a species. In assessing toxicity, the sponsor used as high a concentration as feasible, and no dose-limiting toxicity was found. Dr. Tuan added that different cell types respond to rhBMP-2 with

different types of dose response and that it might be useful to give the panel information about the local concentration of rhBMP-2 at various tissue sites as a function of time. Dr. Riedel said that animal studies have indicated that consistently, 0.10 percent of the implanted rhBMP-2 becomes systemically available—the exposure is very low.

Dr. Diamond said that the antibody assay represents arbitrary numbers and that maternal antibodies can cause prenatal and postnatal problems. She asked numerous questions about how the dose of rhBMP-2 was determined as well as several questions about the sponsor's antibody studies; Drs. Riedel and Boden and Bonnie Roop **[sp?]** of Wyeth-Genetics Institute provided additional clarification to her satisfaction. Dr. Diamond indicated that a pregnancy registry seemed like a good idea and asked how many pregnancies would be needed to produce useful results. Dr. Lipscomb indicated that in any given year, 2,500 women of childbearing age would receive the InFUSE implant; of those, 275 would become pregnant and 2 would develop rhBMP-2 antibodies. Because of the small numbers, a registry might not be appropriate. Dr. Diamond said that the small numbers underscored the importance of studying the effects of antibodies on pregnancy outcomes in animal studies.

Dr. Hanley noted that he had nonvoting status for this meeting. He stated that radiographic issues do not have great pertinence; the main issues are those of labeling, indications, and use of the device.

Dr. Siegal asked whether veterinary or human pathologists had been used in the studies, whether they worked for the company or were independent, and whether they were experts in bone disease. He noted that two pancreatic cell lines showed increased proliferation and one patient had a pancreatic carcinoma—was that coincidence? Through biopsy it should have been possible to obtain enough cells from the patient who developed pancreatic cancer to find out

whether rhBMP-2 played a role. Dr. Lipscomb replied that the number of tumors was less than one would expect in a normal population. Dr. Riedel said that the animal studies were conducted using a contractor and that he could not recall whether the histologist was board certified, but he believed he was. Dr. Siegal also asked why the sponsor could not provide already hydrated rhBMP-2; Dr. Riedel replied that it was because of technical manufacturing issues.

Dr. Kirkpatrick asked how complete the data were beyond 24 months. He also asked for information on the normal expression of BMP in the course of fusion and what liver impairments would prevent metabolism of the enzyme. He expressed concerns about how to guard against off-label use. Dr. Kirkpatrick asked whether the sponsor had identified specific reasons why patients in the control group developed antibodies to bovine collagen, and Dr. Boden responded no. Dr. Boden provided clarification concerning the data beyond 24 months and the follow-up intervals to Dr. Kirkpatrick's satisfaction

Dr. Finnegan asked for more information about why cases that failed did so. Dr. Boden indicated that radiographic failure could be observed in patients who had fused but had reoperation for other reasons. Dr. Finnegan also asked for clarification concerning the difficulties with packaging the three components together. Dr. Lipscomb provided additional information on the sizes of the cages and sponges and how they are used together.

Dr. Naidu pointed out that an antibody response occurred in only three patients and that it appeared that hardly any rhBMP-2 crossed the placental barrier. He reiterated Dr. Reddi's observations that BMPs are normal substances in the body and stated his belief that the product is safe and effective. He asked whether the manual would include additional details regarding perforating the annulus; Dr. Boden indicated that the manual was already fairly detailed.

Dr. Boyan asked for additional information on mineralization and assessment using CT versus x-ray—it is difficult to determine whether something is bone or remineralized collagen early on. Was it possible for elderly people or people who have multiple experiences with the device to develop sensitivity to type-1 collagen or rhBMP-2? Judy O'Grady, regulatory affairs, Integra Life Sciences Corporations (the ACS manufacturer), noted that in the 21-year history of the ACS, no immunogenic response or allergic reaction has been seen. Dr. Boyan asked Dr. Riedel whether any of the animal studies had looked at specific immunological markers, and he responded that they had not.

Dr. Reddi said that much research in cell lines means nothing for patients; tumorigenicity studies must be done in living animals. He asked whether any long-term effects on mice or rats had been studied to determine any in vivo tumorigenic actions. Dr. Riedel said that none of the animal models revealed any evidence of abnormal cell events. Dr. Reddi asked additional clarifying questions concerning the formation of and role of antibodies to rhBMP-2, which Bonnie Rupp answered to his satisfaction.

Dr. Lenchik noted that the quality of the CTs varied widely and that some were uninterpretable. He asked for an explanation of the lower rates of fusion, as assessed by CT, at 24 months versus 12 months, for additional information about the need for a posterior anatomical barrier between the annulus and the cage, and how to treat patients with annular tears or herniation. Dr. Boden responded that the normal population has a high frequency of tears and that those conditions all existed in the clinical trials because they were done with a normal population. No patients formed bone posterior to the cage outside the confines of the disk space. Dr. Boden responded that the drop in the apparent fusion rate at 24 months was due to second surgery criteria. Lenchik asked whether any quantification was used in radiographic assessment,

and Dr. Boden answered that although a grading system had been created in the pilot study, it was determined that the scheme was not useful.

Dr. Larntz noted that the patients in the laparascopic group had differences in baseline variables from the other groups and asked whether any adjustments to the analysis had been made as a result of those differences. Dr. Lipscomb described the sponsor's adjustments.

Dr. Rue observed that although women in the study had agreed not to get pregnant for 16 weeks, six pregnancies occurred. She added that most pregnancies are unplanned and that most women do not know that they are pregnant right away; how did the sponsor suggest handling that situation? She asked whether any patients in the clinical trials had hepatitis and how that affected the outcome; Dr. Lipscomb provided additional data in response.

Ms. Maher said that most surgeons know when fusion occurs and that the issue should be avoided in labeling. With regard to off-label use, she urged caution about trying to mandate the practice of medicine. Surgeons know what is needed and will make that determination on their own regardless of the labeling. Mandating packaging would increase the cost to the consumer.

Dr. Kostuik asked for clarification concerning the urogenital adverse events. Dr. Mathews explained that the patients who did not require autograft had less pain or went home earlier than their InFUSE device or laparascopic counterparts; as a result, their catheters were removed earlier, which in turn affected the rate of urogenital problems.

**OPEN PUBLIC SESSION**

Tushar Patel, Depuy Acromed, a consultant to Striker Biotech and clinical assistant professor at Yale School of Medicine, raised two questions: (1) How does one guard against off-label application of the device? (2) Were any tests done to detect antibodies to rhBMP-2?

**Question 1: Discuss the potential for an immune response in the mother to effectively block**

**BMP-2 expression in the developing fetus.**
The panel concurred that information was not sufficient to answer the question one way or the other. The labeling should perhaps say that patients should be aware that immune response is a possible issue, particularly for pregnant women.

**Question 2: Discuss the potential that the fetal expression of BMP-2 could restimulate a maternal immune response and cause adverse effects in the mother.**
The panel indicated that it was unclear whether the transplacental model goes in both directions. Dr. Miller noted that the data from mouse models suggest that the immune reaction may be only maternal, not fetal. The panel concurred that postmarket study of the issue should be encouraged.

**Question 3: Discuss the potential for rhBMP-2 to stimulate growth of transformed cells.**
The panel agreed that it was not necessary to conduct further studies on transformed cells and that in vivo data are most important at this point.

**Question 4: Comment on the interpretation of the radiographic findings at various timepoints in view of presence/resorption rate of ACS, progression of bone repair in the presence or absence of rhBMP-2, and the relative ability of bone formed at various timepoints to withstand applied loads.**
The panel noted that ACS is absorbed within 6 weeks, so it has little bearing on radiographic findings. The loads are shared by the graft and the titanium cage. The data are insufficient to answer the last part of the question.

**Question 5: Provide suggestions for adequate instructions for use with respect to radiographic interpretation. Discuss any other specific training that should be implemented.**
Dr. Hanley noted that the question pertains to the normal clinical practice of medicine and is not specific to any device. Dr. Finnegan noted that if the cage and the sponge/rhBMP-2 solution were not packaged together, the amount of rhBMP-2 could be inadequate, overadequate, or appropriate for a given cage and patient. Ms. Maher noted that packaging everything together would create additional expense for consumers. Dr. Boden said that surgeons needed the ability

to mix and match. He noted that the sponge can only hold so much rhBMP-2 and could not see why a surgeon would try to use two sponges or additional rhBMP-2.

**Question 6: FDA believes that additional animal models may be useful for assessing an immune response effect on fetal growth and development. Comment on the need for these studies, the types of studies to be performed, and appropriate animal models.**
The panel concurred that studies of antibodies to rhBMP-2 in mouse models would be appropriate.

**Question 7: FDA and the sponsor have agreed to conduct additional nonclinical studies to evaluate the potential for rhBMP-2 to stimulate transformed cells. Comment on the need for any other nonclinical studies, the types of studies to be performed, and appropriate models.**
Dr. Reddi stated that additional study of transformed cell lines is worthless and that simple animal models would be more appropriate. The panel concurred that study of cell lines was not useful at this point.

**Question 8: Comment on the use of ongoing postmarket registry databases to further assess the potential for congenital abnormalities. If registries are recommended, discuss the types of data to be captured.**
Dr. Larntz noted that registries are difficult to conduct well and that the number of potential patients would be too small in this case.

**VOTE**
Dr. Kirkpatrick moved, and Dr. Larntz seconded, that the PMA be approved with conditions.

The panel voted unanimously to approve the PMA with the following conditions:

?? That the sponsor study rhBMP-2 in systemic administration mouse models for antibodies at conception, implantation, and limb bud formation time points (postapproval study)

?? That the sponsor study equal dosing and multiple dosing of rhBMP-2 in mouse models over a long time to complement a large dose at a single time (postapproval study)

?? That the sponsor assess the potential of rhBMP-2 to promote growth of primary tumor isolates that have been analyzed for rhBMP-2 receptor expression (postapproval study)

?? That the FDA approve the PMA for tapered cages only.

The panel also considered requiring that the cage and the sponge/rhBMP-2 solution be packaged together and discussed including a condition that the sponsor conduct postmarket surveillance using a registry. It ultimately decided not to require those conditions because they would not address the panel's concerns regarding off-label use and problems with fetal development. Dr. Larntz summarized the panel's reasons for approving the PMA with the conditions by saying that it was the panel's opinion that the device met the criteria for safety and effectiveness and that the conditions are appropriate to making the device safe and effective. The panel members concurred with his summary.

**ADJOURNMENT**
The panel adjourned at 5:30 p.m.

I certify that I attended this meeting of the Orthopaedics and Rehabilitation Devices Advisory Panel on January 10, 2002, and that these minutes accurately reflect what transpired.

_____
Hany Demian, M.S.
Executive Secretary

I approve the minutes of the January 10, 2002, meeting as recorded in this summary.

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Maureen Finnegan, M.D.
Acting Chairperson

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